Remarks. Entry of the present amendment and reconsideration of the claims is requested. Claims 2, 3 and 6-29 are pending. Each of the amendments to the claims has written support in the specification; accordingly, no new matter has been added to the application.

Written support for amended claims 2, 3, 9 and 18, with respect to the medical disorders listed, appears in the specification, for example, at page 5, lines 12-15. The remaining amendments make only minor, formal changes which clearly do not add new matter.

Written support for new claims 19-29 appears in the specification, for example, at 6-16 as filed.

Telephone Interview of January 4, 2007. Applicants wish to thank examiners Roy P. Issac and S. Anna Jiang for conducting a telephone interview with the undersigned. During the interview, it was agreed that the claims as amended would be compliant with the 35 U.S.C. § 112 (¶1) enablement requirement and the 35 U.S.C. § 112 (¶2) definiteness requirement. The examiners also stated that they would consider the arguments set forth below regarding the rejections under 35 U.S.C. § 103.

Claim objections. The examiner took the position that claims 1 and 17 are identical in scope and required deletion of one. This objection is moot since amended claim 17 properly depends from and is narrower in scope than claim 2. Withdrawal of the objection is appropriate. Such action is requested.

Claim rejections under 35 U.S.C. § 112 (¶1). Claims 1-18 stand rejected as not being compliant with the enablement requirement. The examiner took the position that a practitioner of ordinary skill in the art would not have been able to practice the claimed methods without undue amounts of experimentation. The examiner indicated, however, that

methods for treating familial benign hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, renal secondary hyperparathyroidism, osteoporosis, malignancy-associated hypercalcemia and humoral hypercalcemia of malignancy using a compound represented by a structural formula selected from 1-81 would be enabled (telephone interview and office action at pages 2 and 3). The rejection of claim 1 is moot since the claim has been cancelled.

Although applicants believe that the specification enables claim 1 as filed, applicants also believe that amended claim 2 is compliant with the enablement requirement. In view of the examiner's comments, amended claim 2 should be deemed compliant with the enablement requirement. Amended claim 2 relates to a method for treating the diseases specified above by administering one or more of compounds 1-81. Withdrawal of the rejection is appropriate; such action is requested.

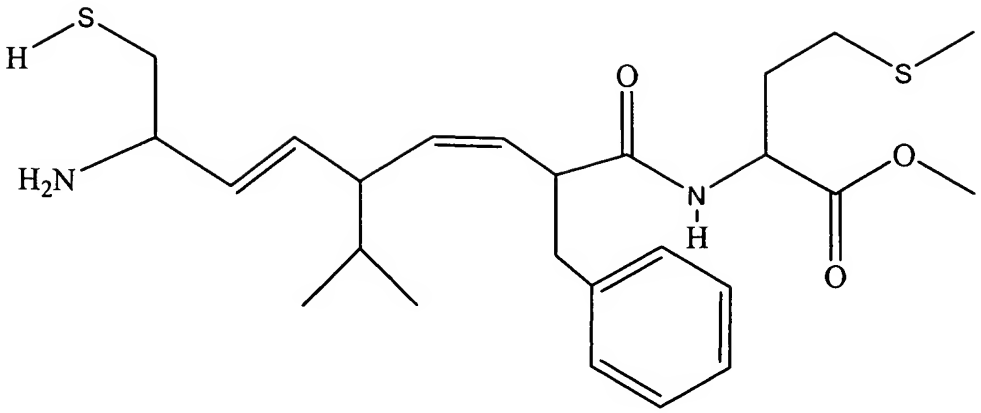
Claim rejections under 35 U.S.C. § 112 (¶2). Claims 1-18 stand rejected as allegedly indefinite. Specifically, the examiner took the position that claims 1, 3, 17 and 18 recite "disorder of calcium homeostasis" and that this is unclear. Applicants point out that the rejection of claim 1 is moot since the claim is cancelled. Moreover, the amended claims no longer recite this phrase. The amended claims recite familial benign hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, renal secondary hyperparathyroidism, osteoporosis, malignancy-associated hypercalcemia and humoral hypercalcemia of malignancy. Each of these disease/disorder descriptions are clear and their meaning would be well known by any practitioner of ordinary skill in the art. Rejection of the amended claims on these grounds would not be proper. Withdrawal of the rejection is requested.

Claim 4 also stands rejected as allegedly indefinite. The rejection is moot since the claim has been cancelled.

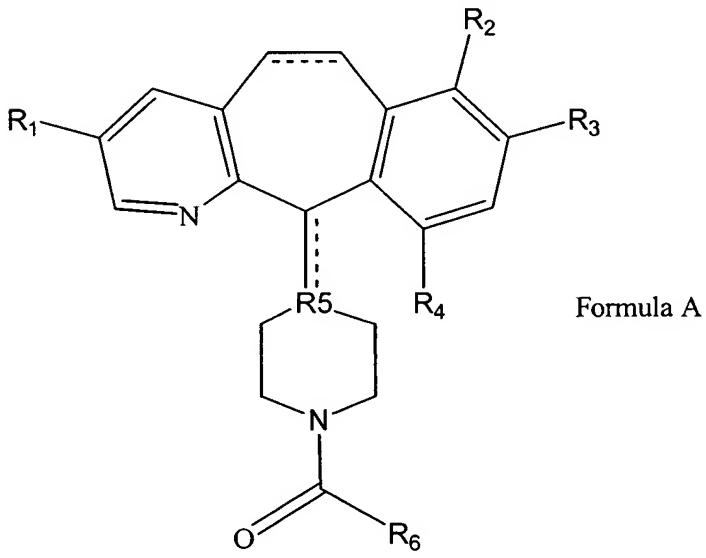
Claim rejections under 35 U.S.C. § 103. Claims 1-8 and 17-18 stand rejected as allegedly obvious over Doll *et al.* (WO 97/23478), Eskins *et al.* (Cancer Treatment Rev. (2000) 26:319-332) and a statement in the instant specification. The examiner stated that Doll *et al.* disclosed the compounds of formula A which are set forth in the claims; that Eskins *et al.* disclosed that the farnesyl protein transferase inhibitor (FTI) B1086 is useful for treating hypercalcemia; and that applicants admitted that there is a relationship between hypercalcemia and FTIs. The examiner took the position that since anti-hypercalcemic effects, effected through Ras, have been observed using FTIs such as B1086, it would have been obvious at the time of invention to use another FTI, such as any of compounds 1-81 or the compounds set forth in claim 18, for the purpose of treating a disorder of calcium homeostasis. Applicants disagree.

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as, in making the modification or combination, there is a reasonable expectation of success in achieving the claimed invention. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In view of the art at the time of the invention, a practitioner of ordinary skill in the art would not have had a reasonable expectation of success in using any of compounds 1-81 or the compounds set forth in claim 18 to treat familial benign hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, renal secondary hyperparathyroidism, osteoporosis, malignancy-associated hypercalcemia or humoral hypercalcemia of malignancy.

The chemical structure of B1086 is set forth below:



(see Nagasu *et al.*, Cancer Res. (1995) 55: 5310-5314 at page 5311-Feb. 4, 2004 Information Disclosure Statement) whereas the compounds in claim 2 are represented by the general chemical formula:



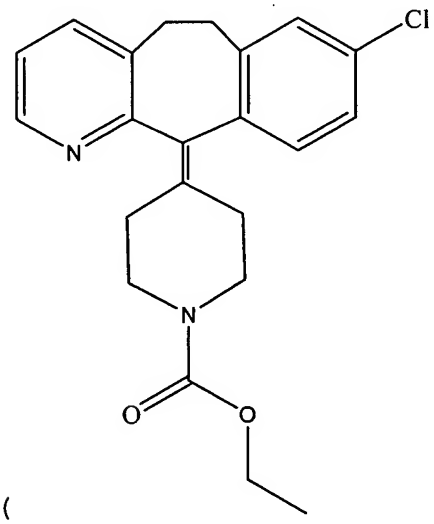
Formula A

A practitioner of ordinary skill in the art would have recognized the fact that two FTI compounds, *entirely unrelated in chemical structure*, shared one biological activity, does not necessarily predict that they will share all other biological activities, even if those biological activities may be mediated through the same target enzyme or receptor. There are a multitude of possible reasons that such a prediction would not be possible to make with the requisite degree of certainty. For example, factors affecting the activity of a

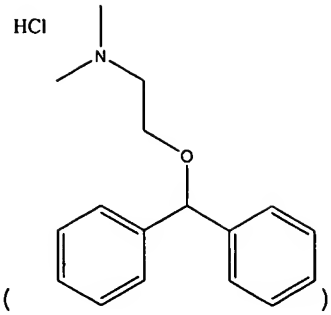
molecule in the body of a patient include the site to which it binds its target enzyme or receptor as well as its binding affinity, the identity and activity of other targets to which it may bind, the molecule's solubility, other biological effects that may be caused by the molecule and others.

Applicants are not, by any means, stating that the art is so unpredictable as to render the claims un-enabled. The examples set forth experiments relating to compound 1 which is highly structurally related to compounds 2-81 and to the compounds set forth in claim 18. The fact that compound 1 is effective at treating the specified disorders is strong evidence that the other, structurally-related compounds (2-81) are also effective in this regard.

A general example of the paradigm discussed above relates to the ability and inability of certain histamine H1 antagonists to alleviate allergic reactions while also not causing sedation. Specifically, loratadine



( ), a well known histamine H1 receptor antagonist, is known *not* to cause sedation when administered. In contrast, the well known, structurally un-related histamine

H1 antagonist, diphenylhydramine HCl (

), *is* known to also cause sedation when administered. This distinction between loratadine and diphenylhydramine exists in spite of the fact that they both inhibit the same histamine receptor and in spite of the fact that the sedating effects of antihistamines are mediated through that same receptor. Exhibit A (Tashiro *et al.*, Life Sci. (2002) 72: 409-414) states in the Abstract section as follows:

> Histamine H1 antagonists, or antihistamines, often prescribed for treatment of allergic disorders, sometimes induce sleepiness and cognitive deficits. It is understood that the mechanism of such CNS side effects is that antihistamine blocks H1Rs in the brain.

Exhibit B (Kay *et al.*, Clin. Exp. Allerg. (1999) 29(3): 147-150) is a report discussing the fact that loratadine and diphenylhydramine are histamine H1 antagonists and that the former is non-sedating whereas latter is sedating.

The examiner's attention is also directed to the enclosed exhibits C & D which are Physician's Desk Reference entries for Claritin® and Benadryl® which are commercially sold drugs containing loratadine and diphenylhydramine, respectively, as the active ingredients. The Claritin® entry indicates that it is "non-drowsy" (circled text) whereas the Benadryl® entry indicates that "marked drowsiness may occur" (circled text).

Thus, a prediction that loratadine was sedating, based on the sedating nature of diphenylhydramine, would have been incorrect. Applicants submit that this type of uncertainty

exists with respect to the *in vivo* effects of structurally unrelated compounds whether they are anti-histamines or FTIs. At the time of invention, a practitioner could not have predicted that any of compounds 1-81 or the compounds set forth in claim 18 were useful in treating any of the specified disorders simply because this effect occurred with respect to B1086. Accordingly, a practitioner would not have had a reasonable expectation of success in testing whether any of compounds 1-81 or the compounds set forth in claim 18 can treat any of the specified disorders.

Similarly, the rejection of claims 9-16 as obvious is improper. These claims properly depend from claim 2 and include all of its elements; thus, the claims are also patentable over the cited art for the reasons discussed above. The additional citation of Nemeth *et al.* does not provide any further proof which could overcome the arguments set forth above with respect to Doll *et al.*, Eskens *et al.* and the statement in the specification.

Applicants submit that the amended claims are patentable over the cited art and request withdrawal of the rejection.

Conclusion:

Early and favorable action is earnestly solicited.

The examiner is invited to contact the undersigned should there by any outstanding questions or concerns regarding the present application.

Respectfully submitted,

Date: Jan. 17, 2007

Thomas Triolo, Ph.D.
Registration No. 48,001
Agent for Applicant(s)

Schering-Plough Corporation
Patent Department; K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033
908-298-2347

EXHIBIT A

ELSEVIER

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Life Sciences 72 (2002) 409–414

Life Sciences

www.elsevier.com/locate/lifescie

Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain

Manabu Tashiro[a,*], Hideki Mochizuki[a], Kentaro Iwabuchi[a], Yumiko Sakurada[a], Masatoshi Itoh[b], Takehiko Watanabe[a], Kazuhiko Yanai[a]

[a] *Department of Pharmacology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai-shi, Miyagi, 980-8575 Japan*

[b] *Division of Nuclear Medicine, Cyclotron and Radioisotope Center, Aoba, Aramaki, Aoba-ku, Sendai, Miyagi, 980-8578 Japan*

Abstract

Brain histamine is involved in a wide range of physiological functions such as regulation of the sleep-wake cycle, arousal, cognition, and memory mainly through interactions with histamine H1 receptors (H1Rs). Neurons producing histamine, histaminergic neurons, are exclusively located in the posterior hypothalamus and transmit histamine to almost all regions of the brain. Histamine H1 antagonists, or antihistamines, often prescribed for treatment of allergic disorders, sometimes induce sleepiness and cognitive deficits. It is understood that the mechanism of such CNS side effects is that antihistamine blocks H1Rs in the brain. The purpose of the present study was to compare the CNS side effects of different antihistamines.

Subjective sleepiness was measured using the Stanford Sleepiness Scale (SSS) and psychomotor performance was examined by a tachistoscope testing system in healthy, young, Japanese volunteers (16 males, 20–28 yrs.) before and after oral administration of antihistamines such as fexofenadine (FEX) and cetirizine (CET). Additionally, H1R occupancy by antihistamines was examined by PET with ^{11}C-doxepin in 8 volunteers.

The results of SSS and psychomotor tests demonstrated that FEX tended to be less sedative than CET though the difference was not statistically significant. PET measurements revealed that no H1Rs in the cerebral cortex were occupied by FEX while about 30% of H1Rs were occupied by CET. In summary, it was confirmed that histamine and H1Rs are involved in maintaining arousal and cognition in humans, and that the severity of clinical symptoms is correlated to the amount of antihistamine that penetrated into the brain.

Keywords: Histamine; Histamine H1 receptor (H1R); Arousal; Cognition; Positron emission tomography (PET); ^{11}C-doxepin

* Corresponding author. Tel.: +81-22-717-8059 or 8057; fax: +81-22-717-8059.
E-mail address: mtashiro@mail.cc.tohoku.ac.jp (M. Tashiro).

0024-3205/02/$ - see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0024-3205(02)02276-2

Introduction

Histamine plays important roles in various physiological functions of the immune, gastrointestinal, and nervous systems. In the immune system, histamine released by mast cells triggers type-I allergic reactions observed in urticaria and seasonal rhinitis (so-called "hay fever"), etc. In the gastrointestinal system, histamine is associated with secretion of gastric acid. In the peripheral nervous system, it is said to be involved in the perception of pain and itchiness. In the central nervous system (CNS), it is associated with a wide range of functions such as in arousal, cognition, learning and memory, regulation of the sleep-wake cycle, appetite control, seizures, aggressive behaviors, emotion, and so on mainly through histamine H1 receptors (H1Rs) [16].

Histaminergic neurons are exclusively located in the tuberomamillary nucleus of the posterior hypothalamus. They project to almost all regions of the brain [15]. Arousal and cognition are among the main roles of brain histamine and H1Rs. Such roles of histamine and H1Rs in humans are well documented by the fact that histamine H1R antagonists, or antihistamines (AH), prescribed for treatment of allergic disorders, often induce sleepiness and deficits in cognitive and psychomotor performance [8,10,13]. It is understood that the mechanism of these CNS side effects is that AHs, penetrating the brain blood barrier (BBB), occupy H1Rs in the brain. Classical first generation AHs often induce significant sedative side effects such as sleepiness and psychomotor deficits, while newer generation AHs are less sedative. Evaluating such CNS side effects of different AHs is of clinical and social importance because these side effects sometimes induce car accidents, etc. Since measurement of subjective sleepiness was not always reliable, various kinds of testing devices have been introduced to measure objectively psychomotor deficits in human subjects. We have developed and have been utilizing positron emission tomography (PET) techniques to understand the roles of H1Rs in the living human brain, too [1,8,9,12,13]. In this paper, we will demonstrate the results of our recent human PET studies using [^{11}C]-doxepin as a radioactive ligand.

Methods

In the present study, subjective sleepiness was measured using the Stanford Sleepiness Scale (SSS) [2] and psychomotor performance was examined using a tachistoscope testing system (Iwatsu, Japan) [8,10] in healthy, young Japanese volunteers (n = 16, ranging 20–28 years old) before and 90 min after oral administration of fexofenadine (120 mg FEX: a non-sedative AH introduced recently), cetirizine (20 mg CET: a slightly sedative second generation AH), both at Japanese maximum doses per day, or hydroxyzine (30 mg HYD: a sedative AH which served as a positive control in this study), in a double-blind placebo controlled crossover design. In this testing procedure, each subject was requested to sit on a chair, facing a computer display in which target stimuli were presented. The subjects were requested to hold a button in each hand and to press a right or left button immediately after the target stimulus appeared on the right or left side of the display, respectively (choice reaction task or CRT), as well as to press the right button each time the target stimulus was presented in the display regardless of its laterality (simple reaction task or SRT). In addition, the subjects were requested to press the right button when Arabic numerals were presented in the center of the display but not when hiraganas (Japanese phonetic alphabets) were presented (character visual discrimination task or CVDT). This CVDT consisted of 4 sessions and exposure duration of Arabic numerals and hiraganas in each session (3,5,7, and 20 milliseconds) was randomized.

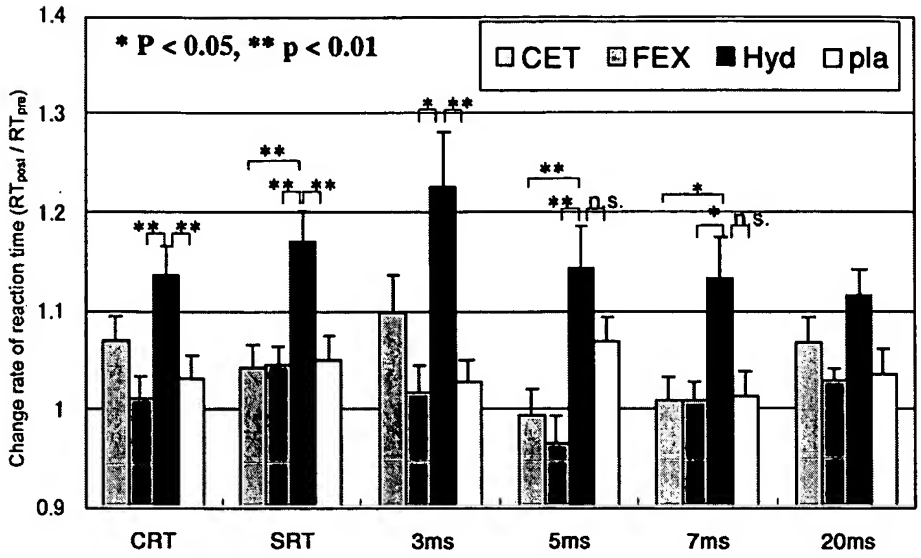


Fig. 1. Results of character visual discrimination task (CVDT). Results of response time (RT) measurement is demonstrated (n = 16). The change rates in RT in each subject was obtained by dividing RT_{post} by RT_{pre}. (* $p<0.05$, ** $p<0.01$. Statistical examination was done by ANOVA followed by multiple comparisons).

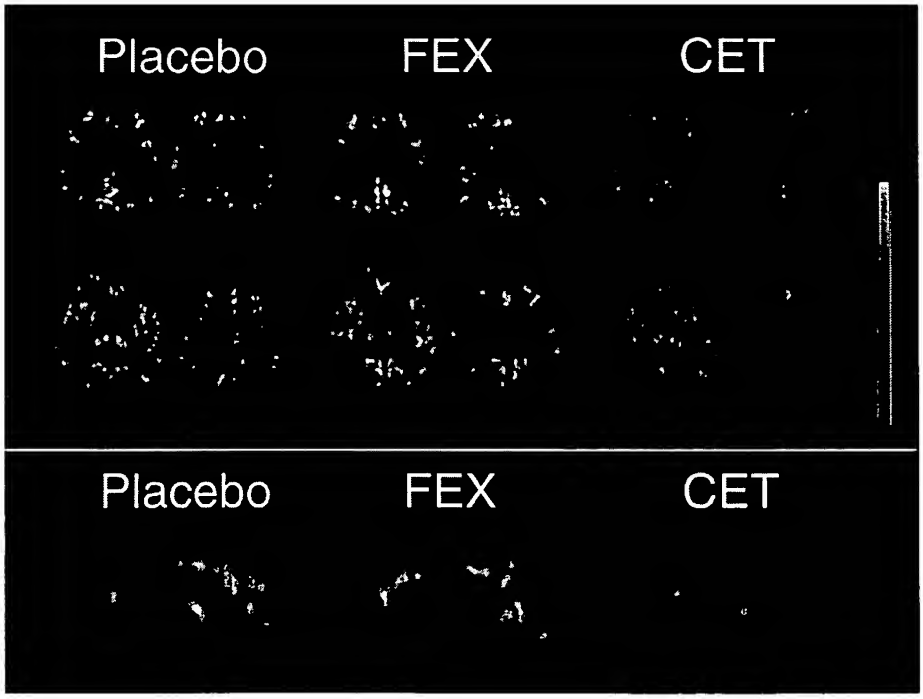


Fig. 2. Brain images demonstrating differences in binding potential due to different antihistamines, fexofenadine (FEX) and cetirizine (CET). Binding potential of FEX is equal to that of placebo, while that of CET is lower than that of both placebo and FEX in transaxial slices (TOP) and sagittal slice (BOTTOM).

Additionally, 10 out of the 16 volunteers were also examined by PET with ^{11}C-doxepin for measurement of histamine H1 receptor occupancy (H1RO). H1RO values for several selected brain regions were calculated from their binding potential (BP) images which were obtained from 90 min dynamic scan images by Logan's graphical analysis [1,8,13]. Finally, scores of SSS, reaction time in psychomotor tests measured by the tachistoscope system, and H1RO measured by PET were statistically examined between FEX and CET using ANOVA followed by multiple comparisons by Glanz test.

Results

The results of the SSS and psychomotor tests demonstrated that FEX seemed to be less sedative than CET though the difference was at threshold level (Fig. 1). PET investigation revealed that almost no H1Rs in the cerebral cortex were occupied by FEX while CET occupied approximately 20 to 50% of H1Rs ($p < 0.01$) (Figs. 2 and 3). Measurement of histamine H1RO by PET seemed to be one of the most reliable techniques to evaluate the CNS side effects of different AHs.

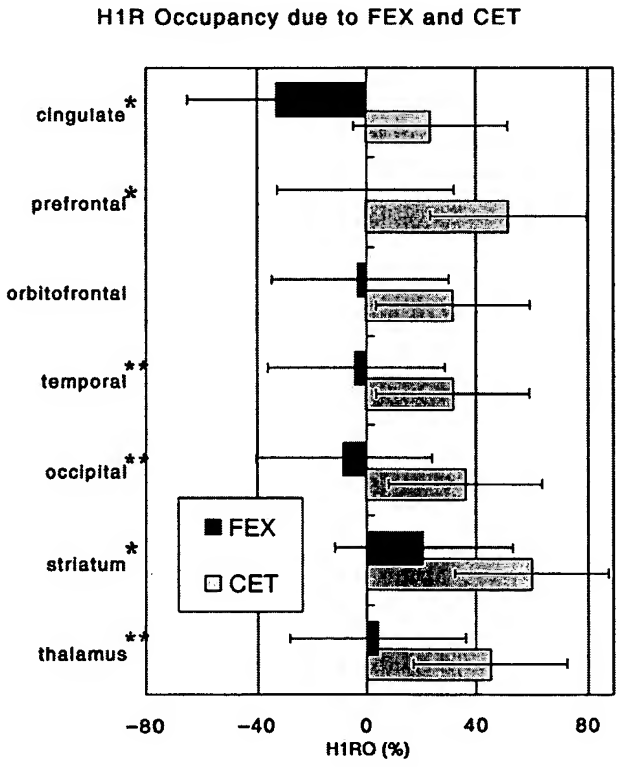


Fig. 3. Comparison of the H1R occupancy (H1RO) of cetirizine (CET) and fexofenadine (FEX). H1R Occupancy (H1RO) was calculated by the following equation: H1RO = [(mean BP in control subjects) - (BP in treated subject)]/(mean BP in control subjects). Most of the H1RO values for FEX are lower than zero and these negative values are interpreted as zero. Appearance of such negative values could be due to inter-subject differences in H1R distribution. *$p<0.05$, **$p<0.01$. Statistical examination was done by Mann-Whitney's test ($n = 8$).

Discussion

Roles of brain H1Rs have been thought to exist in arousal and cognition [8,14], learning and memory (Higuchi et al., 2001), seizures [5], pain perception [6], and so on. To understand the functions of specific proteins such as H1Rs, knockout mice are also very useful and can provide an ideal opportunity to analyze the specific functions of individual mammalian genes. We have also utilized histamine H1R knockout mice to reveal histamine's roles in neurotransmission. Homozygous H1R knockout mice manifested significantly diminished diurnal variation in locomotor activity in contrast to significant variation in wild-type mice [4]. It has been hypothesized that histamine also plays an important role in the abnormal sleep-wake cycle of narcolepsy, based on findings of decreased brain histamine levels in narcoleptic Dobermans [7]. Though hypocretin/orexin might be playing an essential role in this disorder, it was demonstrated that arousal effects of hypocretin/orexin were not observed in H1R knockout mice, suggesting that the histaminergic system was mediating the arousal effects [3]. In this way, scientific investigations on H1R knockout mice have significant merits although the roles of brain histamine equivalent to humans are not always deduced. It would be important to take both animal and human findings into consideration before drawing conclusions on each specific receptor.

For human study, positron emission tomography (PET) is one of the ideal tools that enables us to obtain biochemical and physiological information non-invasively. Recently, measurement of tissue glucose consumption by PET with ^{18}F-fluorodeoxyglucose (FDG) has been used for clinical diagnosis and evaluation of various diseases such as cancer, epileptic seizure, dementia, and ischemic cardiac diseases, as a medical examination mostly supported by health insurance [11]. Additionally, neuro-receptor imaging with PET is very important because no current substitute exists. ^{11}C-doxepin has been a potent molecular tool to visualize distribution of H1R in human brain [12,13]. Our present and previous studies with AHs have demonstrated that histamine is playing very important roles in maintaining arousal and good psychomotor performance in human. In general, newly-introduced second generation AHs occupy 10 to 50% while classical first generation AHs occupy 50 to 80% of H1Rs in the brain [8,9,13]. The recently-introduced fexofenadine (FEX) manifested much lower H1RO (0%) and milder sedation than cetirizine (CET), a typical second generation AH (Figs. 1–3). It is easy to understand that the sedative side effects of AHs are induced by blockade of H1Rs since severity of the side effects correlated to H1RO. Differences in H1RO among different AHs would be because of different permeability of AHs to penetrate the BBB, regulated by influx and efflux proteins such as p-glycoprotein.

In summary, the roles of histamine and H1Rs in arousal and cognition were confirmed previously in knockout mice and currently in human subjects. PET with ^{11}C-doxepin seems to be a more sensitive tool than psychomotor testing for differential comparisons of AHs. The authors would like to stress that non-invasive neuroreceptor imaging in human subjects will be able to find more applications in life sciences of the 21st century, especially when combined with other modalities such as knockout mice experiments.

Acknowledgements

This study was supported by Grants-in-aid from the Ministry of Science, Education and Sports in Japan (to Yanai K and to Tashiro M), and a research grant from Sagawa Traffic Safety Foundation.

References

[1] Higuchi M, Yanai K, Okamura N, et al. Histamine H(1) receptors in patients with Alzheimer's disease assessed by positron emission tomography. Neuroscience 2000;99(4):721–9.
[2] Hoddes E, Zarcone V, Smythe H, et al. Quantification of sleepiness: a new approach. Psychophysiology 1973;10(4):431–6.
[3] Huang ZL, Qu WM, Li WD, et al. Arousal effect of orexin A depends on activation of the histaminergic system. Proceedings of the National Academy of Sciences of United States of America 2001;98(17):9965–70.
[4] Inoue I, Yanai K, Kitamura D, et al. Impaired locomotor activity and exploratory behavior in mice lacking histamine H1 receptors. Proceedings of the National Academy of Sciences of United States of America 1996;93(23):13316–20.
[5] Iinuma K, Yokoyama H, Otsuki T, et al. Histamine H1 receptors in complex partial seizures. The Lancet 1993; 341(8839):238.
[6] Mobarakeh JI, Sakurada S, Katsuyama S, et al. Role of histamine H1 receptor in pain perception: a study of the receptor gene knockout mice. European Journal of Pharmacology 2000;391(1–2):81–9.
[7] Nishino S, Fujiki N, Ripley B, et al. Decreased brain histamine content in hypocretin/orexin receptor-2 mutated narcoleptic dogs. Neuroscience Letters 2001;313(3):125–8.
[8] Okamura N, Yanai K, Higuchi M, et al. Functional neuroimaging of cognition impaired by a classical antihistamine, d-chlorpheniramine. British Journal of Pharmacology 2000;129(1):115–23.
[9] Tagawa M, Kano M, Okamura N, et al. Neuroimaging of histamine H1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. British Journal of Clinical Pharmacology 2001;52(5):501–9.
[10] Tagawa M, Kano M, Okamura N, et al. Differential cognitive effects of ebastine and (+)-chlorpheniramine in healthy subjects: correlation between cognitive impairment and plasma drug concentration. British Journal of Pharmacology 2002;53:296–304.
[11] Tashiro M, Kubota K, Itoh M, et al. Trends in use of positron emission tomography. The Lancet 2001;357(9259):886.
[12] Yanai K, Watanabe T, Yokoyama H, et al. Histamine H1 receptors in human brain visualized in vivo by [11C]doxepin and positron emission tomography. Neuroscience Letters 1992;137(2):145–8.
[13] Yanai K, Ryu JH, Watanabe T, et al. Histamine H1 receptor occupancy in human brains after single oral doses of histamine H1 antagonists measured by positron emission tomography. British Journal of Pharmacology 1995;116(1):1649–55.
[14] Yanai K, Okamura N, Tagawa M, et al. New findings in pharmacological effects induced by AHs: from PET studies to knock-out mice. Clinical and Experimental Allergy 1999;29(Suppl 3):29–36.
[15] Watanabe T, Taguchi Y, Shiosaka S, et al. Distribution of the histaminergic neuron system in the central nervous system of rats; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Research 1984; 295(1):13–25.
[16] Watanabe T, Timmerman H, Yanai K, editors. Histamine research in the new millennium. Amsterdam: Excerpta Medica; 2001.

EXHIBIT B

Clinical and Experimental Allergy, 1999, Volume 29, Supplement 3, pages 147–150

Loratadine: a non-sedating antihistamine. Review of its effects on cognition, psychomotor performance, mood and sedation

G. G. KAY and A. G. HARRIS

Department of Neurology, Georgetown University School of Medicine, Washington, DC and Schering Plough Phase IV Research Unit, Kenilworth, New Jersey, USA

Summary

Although equally potent at blocking the H_1 receptor, first- and second-generation antihistamines can be distinguished with respect to their different effects on the central nervous system (CNS). First-generation antihistamines readily cross the blood–brain barrier leading to significant drowsiness, altered mood, reduced wakefulness, and impaired cognitive and psychomotor performance. This paper reviews of studies CNS functioning conducted with loratadine, a second-generation H_1-receptor antagonist, at its therapeutic dose of 10 mg per day. Studies employing self-report measures, such as diary cards, visual analogue scales, rating scales, and mood inventories have shown that the effect of loratadine on somnolence, fatigue, and mood was comparable to those found with placebo. In studies exploring physiological indices of CNS functioning, such as EEG-evoked potentials, and sleep latency tests, loratadine has been shown to be free of CNS effects. In addition, studies have investigated the effects of loratadine on actual driving performance, and on tests of cognitive and psychomotor functioning. On all of these performance measures, loratadine has been shown to have effects comparable to placebo. In contrast, diphenhydramine, a common first-generation antihistamine, usually available without a doctor's prescription, has significant adverse effects on vigilance, divided attention, working memory and psychomotor performance. Impairment has been shown to occur even in the absence of self-reported sleepiness.

Keywords: CNS functioning, loratadine, cognition, psychomotor function

First generation antihistamines cause significant sedation. Loratadine (Claritin®) a second generation antihistamine was purposely engineered to retain the efficacy of the first-generation H_1-receptor antagonists without the associated sedation and other central nervous system (CNS) effects of the earlier medications. This paper will review the studies which confirmed that the goal of non-sedation and lack of other CNS effects has in fact been achieved.

Evaluations of CNS effects of loratadine have been conducted at the clinically therapeutic dose of 10 mg once daily. Loratadine has a flat dose–response curve for treatment of seasonal allergic rhinitis and urticaria, obviating the need to assess thoroughly CNS sedation at higher doses. Because CNS side-effects can take many forms, studies were conducted to evaluate self-reported changes in drowsiness (or mood), physiologically measured changes in parameters of CNS functioning, and performance measures of changes in cognitive and psychomotor functioning, including changes in performance of a highly demanding task, such as driving.

Correspondence: Dr G.G. Kay, Department of Neurology,Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007, USA.

Self-reported sedation

Determinations as to whether it is appropriate to use the term 'sedating' vs. 'non-sedating' when describing antihistamines are generally based on the drug's adverse event profile (i.e. rate of self-reported somnolence and fatigue) as it compares to the rate of adverse event reporting for subjects treated with placebo during clinical trials. For an antihistamine to be considered non-sedating it is expected to have a sedation rate comparable to, or less, than the observed rate for placebo. If the rate for somnolence or fatigue is higher for the antihistamine than for

placebo, the drug is considered to be sedating. If the antihistamine is determined to be sedating, it is required to carry a warning. The warning alerts consumers that the medication may cause drowsiness and that they need to exercise caution when driving or operating machinery. In clinical trials with loratadine ($n = 1926$) the incidence of somnolence was 8% and the incidence of fatigue was 4% (Ref: package insert). By comparison, in these same trials the incidence of somnolence was 6% and the incidence of fatigue was 3% for placebo ($n = 2545$). Because the rates of reported somnolence and fatigue are considered comparable, loratadine does not carry a warning at its clinically therapeutic dose of 10 mg once daily.

A recent investigation was conducted to further assess the initial and steady-state effects of loratadine on mood and self-reported sleepiness [1]. The study involved 98 healthy volunteers aged between 18 and 51 years. Subjects were randomized into three treatment groups; loratadine 10 mg once daily, placebo, or an initial dose of diphenhydramine 50 mg, followed by subsequent doses of diphenhydramine 25 mg q.d.; all medications and placebo were given for 5 days. Visual analogue scales were used to measure levels of fatigue, motivation, and self-appraised quality of performance. The study also used the ANAM Mood Scale [2], a computerized self-report mood inventory, and the Stanford Sleepiness Scale [3], a seven-point scale on which subjects rate their level of alertness and sleepiness.

Ratings of sleepiness on the Stanford Sleepiness Scale were higher following the initial administration of diphenhydramine than the sleepiness ratings for loratadine ($P < 0.05$) or placebo ($P < 0.01$). Similarly, on the visual analogue scale subjects receiving diphenhydramine reported higher levels of fatigue and lower levels of motivation ($P < 0.01$), and rated the quality of their test performance as being lower compared to subjects receiving loratadine or placebo ($P < 0.01$). Also, compared to subjects taking loratadine or placebo, subjects taking diphenhydramine reported higher levels of fatigue ($P < 0.01$) and lower levels of activity ($P < 0.01$) on the ANAM Mood Scale. Furthermore, results from Day 3 and Day 5 showed that subjects receiving loratadine did not differ significantly from those receiving placebo with respect to level of motivation, depressed mood, or self-appraised quality of performance.

Comparison of the three groups on a composite Sedation/Mood score (derived from the Stanford Sleepiness Scale, ANAM Mood Scale, and visual analogue scales) shows that the subjects who received the 50-mg dose of diphenhydramine reported more sedation and negative mood ($P < 0.01$) than did subjects who received loratadine or placebo. Subjects who received diphenhydramine performed less well than subjects who received placebo on days 3 and 5 on a test of tracking errors that reflects lapses of attention. On day 3 group differences were still evident on self-report measures of mood and sedation ($P = 0.01$). Subjects who received diphenhydramine reported greater fatigue ($P = 0.001$), rated the quality of their test performance as lower ($P = 0.007$), and reported lower motivation ($P = 0.001$) compared with subjects who received loratadine.

The study also investigated the relationship between self-reported sedation and performance (i.e. congitive and psychomotor) measures of sedation. Of the 33 subjects receiving the 50-mg dose of diphenhydramine, 22 did not report a significant change in sleepiness 90-min post-ingestion. Nevertheless, this 'non-sedated' group performed as poorly as the diphenhydramine 50 mg subjects who reported sleepiness and the 'non-sedated' group performed significantly less well than those receiving loratadine or placebo on measures of divided attention, working memory, vigilance and perceptual speed [4].

Physiological arousal

The physiological measures most frequently used to assess CNS depressant effects of antihistamines are the electroencephalogram (EEG), multiple sleep latency test (MSLT) and event related potentials such as the P300 test. EEG has been shown to be sensitive to drug-related changes in vigilance [5,6]. At its therapeutic dose of 10 mg once daily, loratadine has shown no evidence of effects on EEG [6].

The MSLT is an objective, physiological measure of daytime sleepiness that is a common diagnostic tool in sleep disorders clinics and is accepted internationally for quantifying daytime sleepiness after drug treatment, including antihistamines [7]. In a recent study [8], subjects who received either an 8- or 12-mg dose of chlorpheniramine at night in combination with a 60-mg dose of terfenadine in the morning exhibited increased ($P < 0.05$) daytime sleepiness the following day. Subjects who received an 8-mg dose of chlorpheniramine had a mean sleep onset of 6.33 min and those who received a 12-mg dose of chlorpheniramine had a mean sleep onset of 6.87 min. By comparison, those who received placebo had a mean sleep onset of 10.89 min. In contrast, studies conducted by DeRoeck *et al.* [9] and by Roth *et al.* [10] showed no difference between loratadine 10 mg and placebo on the MSLT.

Simons *et al.* [11] used the P300 event-related potential to assess the CNS effects of H_1-receptor antagonists. The P300 test involves having subjects attend to an infrequently occurring tone in the context of a more frequently occurring tone. The EEG event-related response occurring at approximately 300 msec following the onset of 'rare' tones is the P300 wave. The latency of the P300 component

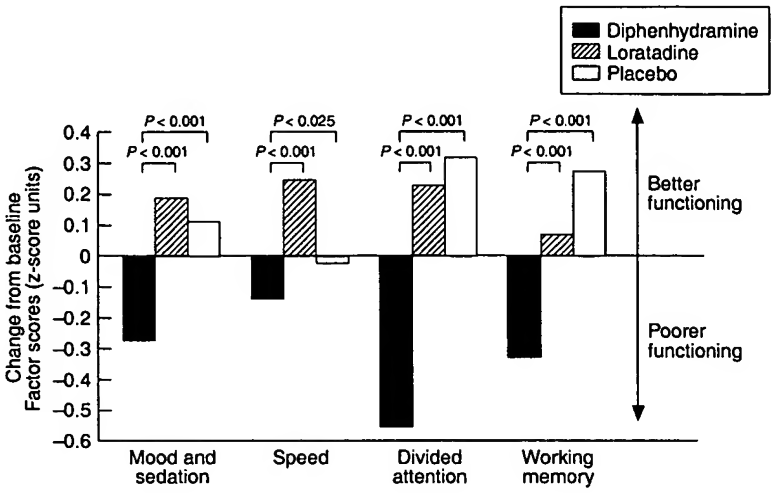


Fig. 1. Principal components (factors) analysis (Day 1). Principal components analyses were done to identify the smallest number of factors that could represent the multiple-dependent measures generated in this study. Twenty-one of the cognitive, psychomotor and self-report variables were selected to exclude overlapping measures for the purpose of data reduction. Five factors resulted: (i) mood and sedation; (ii) speed; (iii) divided attention; (iv) working memory; and (v) vigilance.

increases with CNS depression. Simons *et al.* found an increase in the P300 latency for diphenhydramine (50 mg) compared to baseline and placebo. Subjective somnolence was significantly greater than baseline and placebo after cetirizine (10 mg), ketotifen (2 mg) and diphenhydramine (50 mg). In contrast, loratadine (10 mg) did not cause subjective somnolence or increase the P300 latency.

Cognitive and psychomotor performance

CNS depressant effects can also be revealed by assessment of cognitive and psychomotor functioning. Cognitive test performance refers to an individual's response to testing conditions that require thought processes, such as memory, attention, language, or higher-level reasoning. Psychomotor test performance refers to an individual's responses to test conditions that require skilled (learned) voluntary movement.

The cognitive tests most sensitive to antihistamine-related CNS depression are lengthy vigilance tasks and more demanding measures of divided attention and working memory [12]. Vigilance tasks involve typically the continuous performance of a long, monotonous repetitive task [13]. When performing vigilance tasks, the subject is usually required to sustain a high level of attention in order to detect intermittently occurring, rare events. A decrement in performance on vigilance tasks tends to appear 10–15 min after beginning the task. It is generally agreed that vigilance reflects the extent to which performance on a monotonous task can be maintained, and the extent to which distractions can be resisted. Divided attention tests usually require the subject to perform two or more subtasks simultaneously [14]. Working memory involves the temporary 'holding' of required information while another task is being performed, or while information is undergoing some form of transformation. To the extent that tasks are processed sequentially, divided attention places substantial demands on working memory. Measures of divided attention and working memory are second only to measures of vigilance in demonstrating the detrimental CNS effects of first-generation antihistamines.

Rombaut and Hindmarch [15] reported on an extensive review of cognitive and psychomotor studies with antihistamines. Loratadine (10 mg once daily) was not associated with deficits in cognitive or psychomotor performance in seven out of seven studies reviewed by the authors. Similarly, in a recent study, Kay *et al.* [1] found comparable cognitive and psychomotor performance for subjects receiving loratadine and placebo, following initial dosing and after 5 days of dosing with loratadine (10 mg once daily). In contrast, subjects receiving diphenhydramine

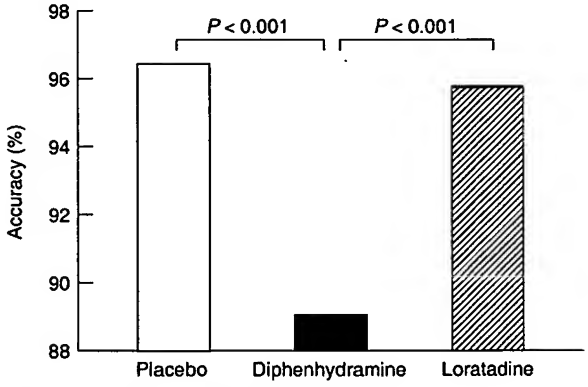


Fig. 2. Day 1 vigilance test results.

(initial dose 50 mg) were impaired on 16 of 18 measures following the initial dose. Subjects in this study were administered a comprehensive computer-based neuropsychological test battery (CogScreen®) known to be sensitive to changes in brain functioning [16] and predictive of actual flight performance of commercial pilots [17].

The adverse effects of diphenhydramine on cognitive functioning was demonstrated on measures of perceptual speed, divided attention, working memory and vigilance whereas, loratadine 10 mg and placebo did not affect any of these parameters.

Based on the impact of sedating antihistamines on self-report instruments, physiological measures, cognitive measures, and psychomotor tests, inferences can be made about the effects that these medications may have on real-world activities. Alternatively, simulators and field studies can provide a more direct indication of the effects of antihistamines on daily activities and job performance. For example, driving simulators and on-road driving tests have demonstrated the CNS depressant effects of antihistamines. According to O'Hanlon [18], 'driving is one of the most complex and demanding tasks performed by the average patient'. O'Hanlon and colleagues developed a specially instrumented automobile for use on a 100-km highway circuit. Equipment in the vehicle measures weaving (i.e. side-to-side motion relative to the painted stripe marking traffic lanes — the standard deviation of lateral position; SDLP). The SDLP index correlates with blood alcohol concentration ($r = 0.89$ [19]). Loratadine (10 mg) did not affect driving performance [6]. In contrast, first-generation antihistamines have been shown to produce a significantly higher weaving index.

Conclusion

In summary, loratadine at its therapeutic dose of 10 mg once daily, has shown no evidence of CNS depressant effects. The effect of loratadine (10 mg) on self-reported somnolence and fatigue, EEG, evoked potentials, MSLT, cognitive and psychomotor testing, and on simulated and actual driving, is comparable to placebo. These findings support the conclusion that Schering Plough accomplished its goal of developing an antihistamine with comparable efficacy to first-generation H_1-receptor antagonists, but without the sedation or other CNS effects of the first generation antihistamines. In summary, freedom from sedation has been demonstrated for loratadine on measures of drowsiness and mood, on physiological measures of attention and sleepiness, and on tests of cognitive and psychomotor performance.

References

1 Kay GG, Plotkin KE, Quig MB, Starbuck VN, Yasuda S. Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine. Am J Man Care 1997; 3:1843–8.
2 Reeves DL, Winter KP, LaCour S, et al. Automated Neuropsychological Assessment Metrics Documentation, Vol. I Test Administration Guide, Silver Springs, MD. Office of Military Performance Assessment Technology 1992.
3 Hoddes E, Zarcone V, Smythe H, Phillips R, Dement W. Quantification of sleepiness. A new approach. Psychophysiol 1973; 10:431–6.
4 Kay GG, Berman B, Harris A. Self-reported sedation doesn't predict impaired CNS functioning after dose of sedating antihistamine. J Allergy Clin Immunol 1999; 103: Abstract 975, S254.
5 Matejcek M. Vigilance and the EEG. psychological, physiological and pharmacological aspects. In: Hermann WM, ed. EEG in Drug Research New York: Gustav Fischer, 1982: 405–508.
6 Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. Eur J Clin Pharmacol 1992; 42:363–9.
7 Nicholson AN, Stone BM. Antihistamines: Impaired performance and the tendency to sleep. Eur J Clin Pharm 1986; 30:27–32.
8 Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood and psychomotor performance. Arch Int Med 1997; 157:2350–6.
9 de Roeck J, Cluydts R, Cosyns P. The sensitivity of methods used for the evaluation of drug induced daytime sedation. J Psychopharmacol 1992; :A6.
10 Roth T, Roehrs T, Koshorek G, Sicklesteel J, Zorick F. Sedative effects of anthihistamines. J Allergy Clin Immunol 1987; 80:94–.
11 Simons FE, Fraser TG, Reggin JD, Simons KJ. Comparison of the central nervous system effects produced by six H_1-receptor antagonists. Clin Exp Allergy 1996; 26:1092–7.
12 Schweitzer PK, Muehlbach MJ, Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. J Allergy Clin Immunol 1994; 94:716–24.
13 Koelega HS. Stimulant drugs and vigilance performance: a review. Psychopharmacol 1993; 111:1–16.
14 Moskowitz H. Attention tasks as skills performance measures of drug effects. Br J Clin Pharmac 1984; 18 (Suppl.):51–61.
15 Rombaut NIE, Hindmarch I. Psychometric aspects of antihistamines: a review. Hum Psychopharmacol 1994; 9:157–69.
16 Kay GG, CogScreen (Aeromedical edn). Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc. 1995.
17 Hoffmann CC, Hoffmann KP, Kay GG. The role that cognitive ability plays in CRM, human factors and medicine panel symposium on collaborative crew performance in complex operational systems. Edinburgh, UK: NATO Research & Technology Agency, 1998.
18 O'Hanlon JF. Antihistamines and driving safety. Cutis 1988; 42:10–3.
19 O'Hanlon JF, Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience. Allergy 1995; 50:234–42.

EXHIBIT C

PDR for Nonprescription Drugs® and Dietary Supplements™ entry for

CLARITIN REDITABS 24 HOUR NON-DROWSY ORALLY DISINTEGRATING TABLETS (Schering-Plough)
Brand of Loratadine

Drug Facts:

Active Ingredient

(in each tablet): **Purpose:**

Loratadine 10 mg.....Antihistamine

Uses: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

- runny nose · itchy, watery eyes
- sneezing · itching of the nose or throat

Warnings: **Do not use** if you have ever had an allergic reaction to this product or any of its ingredients.

Ask a doctor before use if you have liver or kidney disease. Your doctor should determine if you need a different dose.

When using this product do not take more than directed. Taking more than directed may cause drowsiness.

Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions:

- place 1 tablet on tongue; tablet disintegrates, with or without water

adults and children 6 years and over	1 tablet daily; not more than 1 tablet in 24 hours
children under 6 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Other Information:

- safety sealed: do not use if interior foil pouch or individual blister unit imprinted with Claritin® RediTabs® inside the foil pouch is open or torn
- store between 20°C to 25°C (68°F to 77°F)
- keep in a dry place
- use within 6 months of opening foil pouch

- use tablet immediately after opening individual blister

Inactive Ingredients: citric acid, gelatin, mannitol, mint flavor

How Supplied: Boxes of 4, 10, and 20 tablets

Questions or comments?

1-800-CLARITIN (1-800-252-7484) or **www.claritin.com**

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.

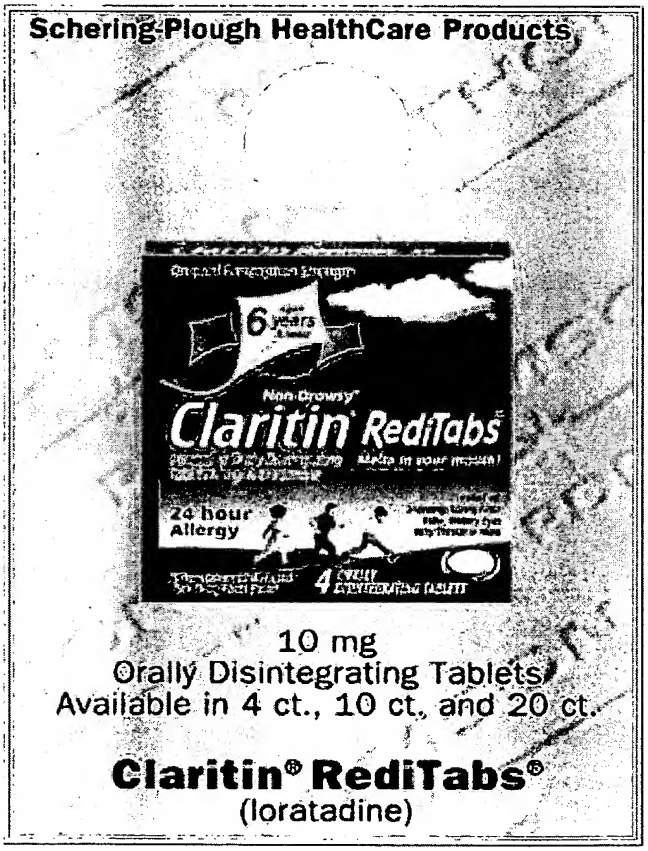


EXHIBIT D

PDR for Nonprescription Drugs® and Dietary Supplements™ entry for

BENADRYL® Allergy
Kapseals® Capsules
(also available in Ultratab™ Tablets) (Pfizer Consumer Healthcare)

Drug Facts:

Active Ingredient: Purpose:

(in each capsule)

Diphenhydramine HCl
25 mg — Antihistamine

Uses:

- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
  - runny nose
  - sneezing
  - itchy, watery eyes
  - itching of the nose or throat
- temporarily relieves these symptoms due to the common cold:
  - runny nose
  - sneezing

Warnings:

Do not use with any other product containing diphenhydramine, even one used on skin.

Ask a doctor before use if you have

- glaucoma
- trouble urinating due to an enlarged prostate gland
- a breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product

- marked drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery
- excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions:

- take every 4 to 6 hours
- do not take more than 6 doses in 24 hours

adults and children 12 years of age and over	25 mg to 50 mg (1 to 2 capsules)
children 6 to under 12 years of age	12.5 mg ** to 25 mg (1 capsule)
children under 6 years of age	ask a doctor
**12.5 mg dosage strength is not available in this package. Do not attempt to break capsules.	

Other Information:

- store at 59° to 77°F in a dry place
- protect from light

Inactive Ingredients: Capsules: D&C red no. 28, FD&C blue no. 1, FD&C red no. 3, FD&C red no. 40, gelatin, glyceryl monooleate, lactose, magnesium stearate, and titanium dioxide. Printed with black edible ink.

Tablets: candelilla wax, crospovidone, dibasic calcium phosphate dihydrate, D&C red no. 27 aluminum lak hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, stearic acid, and titanium dioxide.

Questions? call **1-800-524-2624** (English/Spanish), weekdays, 9 AM-5 PM EST

How Supplied: Benadryl tablets are supplied in boxes of 24 and 48, bottles of 100 and 124; capsules are supplied in boxes of 24 and 48.